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Secular Trends in Outcomes for Fanconi Anemia Patients Who Receive Transplants: Implications for Future Studies

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ABSTRACT

Transplantation protocols for patients with Fanconi anemia are being modified continuously. However, it is unclear how outcomes have changed over time. We determined historical adverse event rates from long-term follow-up of 117 Fanconi anemia patients in the Hôpital Saint Louis transplant cohort, who received low-dose cyclophosphamide- and irradiation-based conditioning, in combination with other modalities, between 1976 and October 2002. In high-risk patients with mismatched donors, the peritransplantation mortality rate during 0 to 6 months declined significantly over time ($P = .003$), from 28%/month (95% confidence interval [CI], 9%-87%/month) during 1985 to 1989 to 3.3%/month (95% CI, 0.8%-13.3%/month) during 2000 to October 2002. The corresponding proportion of patients who developed severe acute graft-versus-host disease also declined significantly over time ($P = .003$). In low-risk patients with matched sibling donors, the peritransplantation mortality rate was consistently low, 1.4%/month (95% CI, 0.3%-5.3%/month), during 1990 to October 2002. Sample sizes to detect 2-fold reductions from rates and risks observed since the mid-1990s are larger than recently reported case series. To demonstrate further advances in survival, transplant centers may need to coordinate their protocols and engage in multicenter collaborative studies.

KEY WORDS

Fanconi anemia • Stem cell transplant • Risk assessment • Study design • Statistics • Numerical data

INTRODUCTION

Fanconi anemia (FA) is a genetically heterogeneous genomic instability syndrome [1] associated with diverse congenital abnormalities, progressive bone marrow failure, acute myeloid leukemia, and solid tumors [2]. Hematopoietic stem cell transplantation is the only current therapy that can restore normal hematopoiesis in patients with FA. The cumulative incidence of bone marrow transplantation, death secondary to progressive bone marrow failure, or acute myeloid leukemia was 64% by age 48 years in the North American Survey [3]; all of these patients either received a transplant or developed indications for one.

It has been challenging to adapt protocols for transplantation to the setting of FA [4]. Because of their underlying defect in DNA repair, FA patients are hypersensitive to treatment with irradiation and cytotoxic agents such as cyclophosphamide. Pretransplantation conditioning regimens modified for FA patients have met with some success. At present, outcomes for FA patients with a matched sibling donor are quite good; however, results for patients with other donor types are comparatively less successful [5]. Several potential complications put patients at an increased risk of early death, including acute and chronic graft-versus-host disease (aGVHD and cGVHD, respectively). In long-term survivors, the incidence of secondary solid tumors, particularly squamous cell

cancers (SCC) of the head and neck, has been an ongoing concern [6]. Severe aGVHD (grades III plus IV) and extensive cGVHD are associated with SCC in patients who survive these transplantation complications [5,7].

There is considerable interest in novel improved and "gentler" transplantation protocols for FA patients to increase survival and decrease aGVHD, cGVHD, and, it is hoped, secondary SCC. Several innovations have been considered, including regimens with less or no irradiation or cyclophosphamide; new conditioning agents such as antithymocyte globulin (ATG), fludarabine (FLU), and Campath (Schering Plough, Oxford, UK); graft manipulations such as $CD34^+$ stem cell selection; and alternative sources of stem cells rather than bone marrow [8-12].

Several of these innovations have been piloted or tested in small patient series over the years, and standards of care have evolved to include some of these modalities, such as ATG and FLU. However, it has proven difficult to determine the best approaches. The issue of statistical power is a fundamental problem. Because FA is a rare disease, transplantation protocols for FA patients have been institution specific, each with a comparatively low rate of patient accrual, even at the largest transplant centers. Consequently, these studies have not been randomized [13].

To help investigators who are planning future transplantation studies for FA patients, we asked 3 related questions. First, have outcomes improved over calendar time in concert with changes in the standards of care? Second, what are the relevant study end points and corresponding historical control rates that might be used to evaluate emerging therapies? Third, what sample size is required to prove that a new regimen is superior to a standard?

By necessity, historical control rates are needed to calculate the statistical power at a given sample size. For this purpose, we identified relevant study end points and determined historical control rates by using long-term follow-up of 117 FA patients who received transplants at the Hôpital Saint Louis (SLH) in Paris, France [5]. The SLH cohort is the largest published series of FA patients who had transplantations performed by a single team at a single institution. We also performed a literature review to determine the sample sizes of recently reported studies of FA patients who received transplants and evaluated the power of these studies in light of our sample size calculations.

METHODS

Historical Control Rates in SLH

We previously studied long-term follow-up of 117 FA patients who received transplants at the SLH [5]. Analytical studies of a subset of these patients with mismatched [14] and matched [7] donors have also been reported. Almost all of these patients were conditioned with low-dose cyclophosphamide and irradiation. Several groups have adapted the original protocol for use in their own institutions. Similarly, SLH protocols have evolved over time to include other modalities, including ATG and FLU. In this series of 117 patients, 5 received transplants in 1976 to 1979, 14 in 1980 to 1984, 15 in 1985 to 1989, 69 in the 1990s, and 14 in 2000 to October 2002. We chose to exclude from our analysis the earlier years 1976 to 1984, because protocols and supportive care have advanced considerably since then. Therefore, we propose here to use the SLH experience with 98 patients who received transplants during 1985 to October 2002 as an indicator of trends over time in the field as a whole, recognizing that both patients and protocols are heterogeneous.

We stratified this cohort into groups of patients who received transplants during 4 calendar periods: 1985 to 1989, 1990 to 1994, 1995 to 1999, and 2000 to October 2002, henceforth "2000 to 2002." On the basis of our previous analysis, we considered 5 patient groups and end points for analysis: the cumulative incidence of death at 6 months in patients with a mismatched (matched unrelated or mismatched related) donor (high-risk patients) and in patients with a matched sibling donor (low-risk patients); the cumulative incidence of severe aGVHD at 100 days; and the cumulative incidence of SCC at 10 years. For the end point of peritransplantation mortality, we calculated the mortality rate from tables of person-years and numbers of deaths for the defining 0- to 6-month follow-up interval according to patient group and the calendar period of transplantation. For the end point of severe aGVHD, we calculated the proportions of patients who developed this complication during 0 to 100 days according to patient group and the calendar period. Because the numbers of SCC cases were comparatively limited and the first case appeared 5 years after transplantation, we calculated the cumulative incidence of SCC through 10 years in all patients who received transplants during 1990 to 1999.

For the end point of peritransplantation mortality, we examined rates and trends by using Poisson regression. For the end point of severe aGVHD, we examined risks and trends by using logistic regression. For the end point of SCC, we considered the cumulative incidence at 10 years in the presence of competing mortality. Finally, as a general indicator of advances in protocols, we tabulated the frequency of specific modalities over time. Because the focus of this analysis is calendar time trends and sample size calculations, we did not examine the relationship between specific modalities and outcomes for this article. Some of the specific associations have been reported elsewhere [14].

Sample Size Calculations

We computed the required sample size for a binomial test comparing the cumulative incidence observed in a new series with the cumulative incidence observed in the SLH. We set the type I error rate (false-positive rate) to $\alpha = .05$. We set the type II error rate (false-negative rate) to $\beta = .20$, corresponding to 80% power. All tests were 2 sided. We defined null and alternative hypotheses as follows. From SLH, we obtained the monthly event rates λ_0. For example, in the entire cohort, the monthly death rate during 0 to 6 months was 7.1%/month [5]. Assuming a constant hazard rate, the cumulative mortality at landmark time $T = 6$ months equals

$$p_0 = 1 - \exp(-\lambda_0 T).$$

Suppose a new protocol is to be tested in the hope that it will cut the monthly death rate in half, from λ_0 to λ_1 ($\lambda_1 = \lambda_0/2$). The factor of 1/2 corresponds to the parameter θ, the treatment relative risk. A value of $\theta = 1/2$ represents a 2-fold reduction in the hazard, whereas a value of $\theta = 1/4$ represents a 4-fold reduction, and so on. In this scenario, the cumulative mortality will not be p_0, but instead will be

$$p_1 = 1 - \exp(-\lambda_0 \theta T).$$

Let n be the number of patients enrolled and followed up through time T. Let X be the number who have the event "death during 0 to 6 months." Under the null hypothesis (H0) that a new protocol has the same efficacy as the SLH protocol, X follows the binomial distribution $X \sim \text{Bin}(n,p_0)$. For sample size calculations, we ask how large n must be to reject H0 if $X \sim \text{Bin}(n,p_1)$.

To compute the required sample size, we invoked the normal approximation to the binomial distribution and applied the standard formula [15]:

$$n = \frac{p_0 q_0 \left(z_{1-\alpha/2} + z_{1-\beta} \sqrt{\frac{p_1 q_1}{p_0 q_0}} \right)^2}{(p_1 - p_0).^2},$$

where $q_0 = 1 - p_0$, $q_1 = 1 - p_1$, and z_γ is the $100(1 - \gamma)$ percentile of the standard normal distribution.

We also considered the reverse problem of determining the smallest detectable fold- reduction θ for a given n. We computed these values as follows. First, the critical values of the test under the null are

$$c_L = np_0 - \sqrt{np_0 q_0 z_{1-\alpha/2}}$$

and

$$c_U = np_0 + \sqrt{np_0 q_0 z_{1-\alpha/2}}.$$

Under the alternative,

$$Power = \Phi(Z_L) + 1 - \Phi(Z_U),$$

where

$$Z_j = (c_j - np_1)/\sqrt{np_1 q_1},$$

$j = L,U$, and $\Phi(.)$ is the cumulative standard normal distribution. The values of power can be evaluated as a function of p_1 with n and all other parameters fixed. The value of p_1 that minimizes $[Power(p_1) - 0.80]^2$, $p1,min$, was found numerically (by using a golden section search and parabolic interpolation), and the corresponding value

$$\theta_{\min} = \log(1 - p_{1,\min})/\log(1 - p_0)$$

For small n and p_0, the expected number of events may be fewer than 5, and the normal approximation may not be valid. In these instances, we calculated the critical values and power by using an exact binomial test. All calculations were performed with MATLAB version 7.0 (MathWorks, Natick, MA).

Literature Review

The medical literature was searched by using MEDLINE for all patients with FA who received a transplant. The search was supplemented after the bibliographies of each publication were reviewed. The analysis was restricted to studies published between 1999 and 2004. The search terms were "Fanconi's anemia," "Fanconi anemia," or "aplastic anemia." Information about individual studies was entered into an Excel spreadsheet (Microsoft, Redmond, WA), which was used to tabulate characteristics of patient series and case reports.

RESULTS

Trends in Transplantation

Transplantation protocols have advanced over time (Table 1), particularly for patients with a mismatched donor. Initially, almost all patients received low-dose cyclophosphamide and irradiation. In high-risk patients with a mismatched donor, ATG was used extensively during 1995 to 2002, and FLU was used extensively during 2000 to 2002. These modalities were used in a smaller proportion of low-risk patients with a matched sibling donor.

Historical Control Rates in SLH

Among high-risk patients with mismatched donors, the peritransplantation mortality rate during 0 to 6 months declined significantly over time ($P = .006$; Figure 1A, left axis) from 28%/month (95% confidence interval [CI], 9%-87%/month) during 1985 to 1989 to 3.3%/month (95% CI, 0.8%-13.3%/month) during 2000 to 2002. The period-specific rates are uncertain (error bars in Figure 1A show corresponding 95% CI). The fitted rate declined by 1.8-fold

Table 1. *Number of SLH Patients Who Received Transplants and Were Treated with Selected Modalities, by Calendar Period*

Modality	1976-1984*	1985-1989	1990-1994	1995-1999	2000-2002†
Matched donor‡					
ATG	1	0	2	1	0
FLU	0	0	0	0	1
BU	0	0	0	1	0
T-cell depletion	0	0	0	0	0
TBI	0	0	0	0	0
TLI	13	11	23	4	0
CY	16	11	23	5	1
n	16	11	23	5	1
Mismatched donor					
ATG	0	1	4	23	9
FLU	0	0	9	0	12
BU	0	0	1	1	7
T-cell depletion	0	0	0	18	0
TBI	0	1	0	21	4
TLI	1	3	16	2	0
CY	3	4	17	24	9
n	3	4	17	24	13

ATG indicates antithymocyte globulin; FLU, fludarabine; BU, busulfan; TBI, total body irradiation; TLI, total lymphoid irradiation; CY, cyclophosphamide.

*These patients are not included in this analysis.

†January 2000 through October 2002.

‡Matched donor is an HLA-identical sibling; mismatched donor is all other donor types.

(95% CI, 1.2- to 2.8-fold) per period from 1985 to 1989 through 2000 to 2002. In this group, the proportion of patients who developed severe aGVHD also declined significantly over time ($P = .003$; Figure 1C, left axis) from 50% (95% CI, 12.3%-87.7%) during 1985 to 1989 to 7.7% (95% CI, 1.1%-39.1%) during 2000 to 2002.

Among low-risk patients with matched sibling donors, the peritransplantation mortality rate during 0 to 6 months (Figure 1B, left axis) was 1.4%/month (95% CI, 0.3%-5.3%/month) during 1990 to 1999. There were no peritransplantation deaths among 6 low-risk patients who received transplants during 1995 to 2002 (rates for 1995 to 1999 and 2000 to 2002 were unstable, and error bars are not shown). The trend over time was not significant ($P = .54$). In this group, the proportion of patients who developed severe aGVHD (Figure 1D, left axis) was stable over time ($P = .71$ for trend). Among patients who received transplants during 1990 to 1999, the proportion who developed severe aGVHD was 17.9% (95% CI, 7.7%-36.4%). Only 1 low-risk patient received a transplant during 2000 to 2002; this patient did not develop severe aGVHD. Among patients who received transplants during 1990 to 1999, the cumulative incidence of SCC by 10 years after transplantation was 15.2% (95% CI, 1.6%-28.7%), similar to the figure of 12.1% (95% CI, 3.7%-20.4%) observed in the entire SLH cohort.

Sample Size Calculations

We computed the sample size required to detect a 2-fold reduction in the peritransplantation mortality rate in high-risk patients (Figure 1A, right axis) and low-risk patients (Figure 1B, right axis) with 80% power, allowing for a 5% false-positive rate. The required sample size increases at a greater than linear rate as the benchmark rate declines; here, the benchmark rate equals the fitted or smoothed rate that allows for a calendar time trend (Figure 1A and B, right axes; dotted blue curves). According to these calculations, 84 high-risk patients, each followed up for 6 months, would suffice to detect a 2-fold rate reduction when the benchmark rate equals 5.5%/month, corresponding to the fitted rate for the 2000 to 2002 period. A smaller number of high-risk patients (n = 49), would suffice when the appropriate benchmark rate equals 10.0%/month, the fitted rate for the 1995 to 1999 period. In contrast, 351 low-risk patients would be needed to detect a 2-fold reduction from the fitted rate in 1990 to 1994 of 1.3%/month, because early deaths are expected to be comparatively rare. The required sample size increases rapidly as the benchmark rate declines below the value of 1.3%/month.

Next, we computed the sample size required to detect a 2-fold reduction in the risk of severe aGVHD in high-risk (Figure 1C, right axis) and low-risk (Figure 1D, right axis) patients. The proportion of low-risk patients who developed severe aGVHD was stable over time (Figure 1D, left axis), whereas the proportion of high-risk patients who developed this complication declined to a similar level by the mid-1990s. If the proportion of patients expected to develop this complication were 15.0% (the time-averaged value for low-risk patients, shown by the horizontal dotted blue

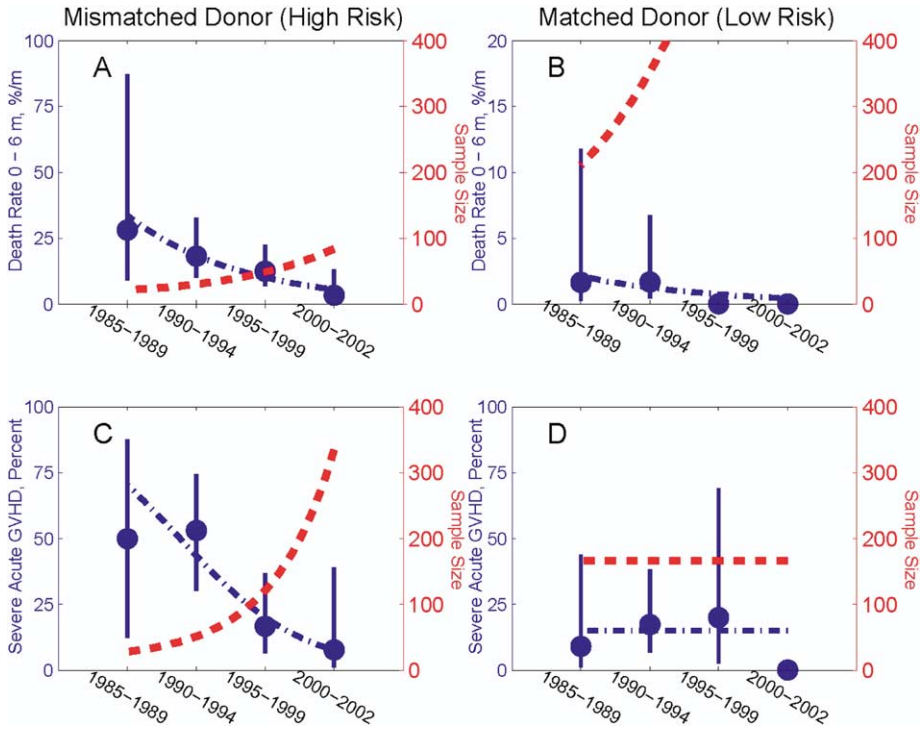

Figure 1. Secular trends in peritransplantation mortality and severe aGVHD in SLH and the corresponding sample sizes needed to demonstrate 2-fold risk reductions. (A, left axis, blue) Monthly mortality rate during the 0- to 6-month follow-up period in patients with a mismatched donor by calendar period. Observed rates (data points) with 95% CI (error bars) and fitted rates allowing for a calendar time trend (dot-dash curve) are shown. (A, right axis, red, dashed curve) Corresponding sample size required to demonstrate a 2-fold rate reduction from the fitted rate with 80% power, allowing for a 5% false-positive rate. (B) Monthly mortality rate (left axis) and sample size to detect 2-fold rate reduction (right axis) in patients with a matched donor. Note the change in the y-axis scale between A and B (left axes). (C, left axis, blue, data points, error bars, and dot-dash curve) Proportion of patients with a mismatched donor who developed severe aGVHD, by calendar period. (C, right axis, red, dashed curve) Sample size required to detect a 2-fold risk reduction from the fitted proportion. (D) Proportion of patients with a matched donor who developed severe aGVHD and the corresponding sample size to detect 2-fold risk reduction. In (D), the fitted proportion is constant over time. m indicates months.

curve in Figure 1D, right axis), then 165 patients would be required.

The same number of patients, 165, is needed to detect a 2-fold reduction in the estimated 10-year incidence of SCC, because the cumulative incidence is similar in magnitude: 15.2% at 10 years versus 15.0% at 100 days. This latter calculation implicitly assumes that the competing risk of death would be the same as what was observed in SLH patients who received transplants during the 1990s. If the competing risk of death were lower, then more patients would live long enough to develop SCC, and the power of the study would be higher. However, it would be optimistic to plan a study on the basis of such an assumption.

Finally, we computed the detectable fold- reduction for a given n at 80% power, allowing for a 5% false-positive rate, for selected benchmark values (Table 2). Notably, with as few as 25 high-risk patients with mismatched donors, each followed up for 6 months, a 2.8-fold reduction in the peritransplantation mortality rate could be detected with 80% power. A larger number of patients (n = 100) is required to detect a similar 2.6-fold reduction in the risk of severe aGVHD, because the cumulative incidence of this complication is comparatively lower (15% versus 45%). The same number of patients, each followed up for 10 years, would likely detect a 2.6-fold reduction in the cumulative incidence of SCC.

Literature Review

We found 33 studies of 251 patients (Table 3). The largest 7 studies had from 8 to 69 patients. An additional 26 studies each had from 1 to 4 patients. Of these, 15 were single case reports. Of 251 patients, 129 (51%) received stem cells (usually derived from bone marrow) from a matched sibling, and 122 (49%) received stem cells from other types of donors (mismatched). The conditioning regimens were heterogeneous. Two hundred eight patients (83%) were conditioned with irradiation, and 24 (10%) were conditioned with FLU. ATG was used in 80 patients, busulfan in 4, Campath in 2, T-cell depletion in 59, and $CD34^+$ stem cell selection in 13. No study used randomization.

Excluding SLH, the largest reported series in

Table 2. *Detectable-Fold Reduction for a Given Sample Size*

End Point	Cumulative Incidence	n = 25	n = 50	n = 75	n = 100	n = 200
Mortality 0-6 mo, mismatched donor, 1995-1999 referent	45% at 6 mo	2.8*	2.0	1.7	1.6	1.4
Mortality 0-6 mo, mismatched donor, 2000-2002 referent	28% at 6 mo	5.2*	2.1	2.1	1.9	1.5
Mortality 0-6 mo, matched donor, 1990-1999 referent	7.8% at 6 mo	9.1*	18.2*	9.7	5.3	2.6
Severe aGVHD, matched/mismatched donor, 1995-1999 referent	15.0% at 100 d	18.2*	5.2	3.3	2.6	1.9
SCC, 1990-1999 referent	15.2% at 10 y	18.4*	5.2	3.3	2.6	1.8

*Values were computed with the exact binomial test. Because of the discreteness of the data, the magnitude of the detectable-fold reduction is not a continuous function of n or of the cumulative incidence.

1999 to 2004 had 29 patients. As shown in Table 2, studies of this size are powered to detect major improvements but are unlikely to detect a 2-fold reduction in the rate of any end point shown in Figure 1 or Table 2.

DISCUSSION

Continuous improvements in outcomes (Figure 1) are presumably related to improvements in protocols (Table 1) and in supportive care. In FA patients with mismatched donors, the peritransplantation mortality rate significantly and substantially declined over time, decreasing by approximately 1.8-fold in each of 4 consecutive calendar periods. In the most recent period studied, January 2000 to October 2002, the rate had declined to 3.3%/month. The precise value of this rate is uncertain; however, it clearly represents a dramatic decrease from the rate of 28%/month that held during 1985 to 1989. Overall, the data show a trend toward convergence of results that can be obtained for patients with mismatched and matched donors.

The demonstrated progress in this field is good news—so good, in fact, that it presents a conundrum for future studies. How does one demonstrate further improvements as the rate of adverse events declines? A recent study by Ayas et al. [19] highlights both the optimism and uncertainty that characterize the current protocols. This study of 22 patients with matched donors showed excellent results; however, the authors noted that the optimal doses of cyclophosphamide and ATG remain unclear.

FA is a rare disease, and, consequently, many transplant series have been comparatively small. To prove that a new conditioning regimen offers superior survival compared with the current regimens, our power calculations suggest that centers may now need to use the same protocol in multicenter collaborative studies.

In the literature, approximately half of reported patients were in the high-risk group, defined here as patients without a matched sibling donor. This fraction may be increasing over time. Clearly, reducing the peritransplantation mortality rate in this group is a high priority. It is notable, therefore, that a study of

Table 3. *Published Patient Series and Case Reports of Fanconi Anemia Patients Who Received a Transplant, 1999-2004*

Study*	Year of Report	Donor	N†	XRT	FLU
de Medeiros: Brazil [11]	1999	Matched	16	0	0
Dufour: Italy AIEOP-GITMO [16]	2001	Matched	27	22	0
Ayas: Saudi Arabia [17]	2001	Matched	19	19	0
Guardiola: Paris [7]‡	2004	Matched	37	37	0
15 studies, 1-4 patients§	1999-2004	Matched	30	17	8
MacMillan: Minnesota [18]	2000	Mismatched	29	29	0
Guardiola: Europe [14]‡	2000	Mismatched	69	67	0
Boyer: Cincinnati [9]	2003	Mismatched	8	8	8
11 studies, 1-4 patients‖	1999-2004	Mismatched	16	9	8
33 studies	1999-2004	129 Matched + 122 mismatched	251	208	24

*These 33 patient series or single case reports with matched or mismatched donors were reported in 28 publications. Five authors reported matched and mismatched patients in the same publication; these are treated here as separate studies.

†N indicates the total number of subjects; XRT, the number who received conditioning with irradiation; FLU, the number who received conditioning with fludarabine.

‡These series include patients from the SLH cohort.

§Seven of these 15 studies are single case reports.

‖Eight of these 11 studies are single case reports.

25 high-risk patients, each followed up for 6 months, would suffice to detect a 2.8-fold reduction in peritransplantation mortality with 80% power when the appropriate benchmark rate is 10%/month, corresponding to a cumulative incidence of 45% at 6 months. Eighty-four patients are needed when the appropriate benchmark rate is 5.5%/month. The 122 mismatched cases reported in 14 patient series or single case reports during 1999 to 2004 (Table 3) would have been sufficient to evaluate 2 or 3 promising protocols for a 2- to 3-fold rate reduction, had it been possible to enroll these patients in a few collaborative studies.

A multicenter study approach would have several potential advantages. First, a sequence of nonrandomized observational studies could be conducted [20], each sufficiently large to inform subsequent protocols. The corresponding sample sizes required for randomized studies would be 4 times larger [13] and, therefore, difficult or impossible to attain. Because the end points of development of severe aGVHD at 100 days and mortality at 6 months require only that each patient be followed for up to 6 months, each trial could be completed soon after the target sample size was enrolled. Second, ancillary questions might be better addressed by pooling resources and capabilities. For example, a collaborative study could determine whether the outcomes are associated with complementation group, mutation status, or patient phenotype. Third, results from a multicenter study might be more convincing and generalizable than pooled results from isolated studies, because the protocol itself would represent a consensus.

There are potential disadvantages. In the setting of FA, some aspects of transplantation are as much art as science. The astute clinician can make correct individualized decisions, and centers can incorporate new technology, ahead of definitive data. It is critical that common protocols do not blunt the art in an effort to advance the science. It is also critical that innovative ideas conceived by individual investigators continue to be piloted. The conduct of a multicenter study would also incur additional costs—for example, to harmonize the study informatics and obtain approval by institutional review boards at dispersed institutions. Funding sources will need to be convinced of the value added.

Regardless of the protocol used, FA patients will require lifelong surveillance for cancer. Past transplantation modalities increased the risk of solid tumors above the high Fanconi baseline [5]. Even if new protocols were able to reduce the risk of solid tumors to baseline, which is not clear, the cumulative incidence of solid tumors would remain high and might actually increase over time, as more patients lived long enough to develop tumors. The calculations in Table 2 suggest that to assess changes in cancer incidence will require long-term follow-up of essentially all FA patients who receive a transplant. A registry for this purpose would be informative. A registry might also help to quantify long-term outcomes in patients with matched sibling donors, which requires even larger numbers.

In summary, this may be an appropriate time for the field to consider its strategies. Going forward, the question is whether new protocols are to be evaluated by small studies and retrospective analysis or by prospective multicenter studies. The optimal strategy depends on the expected size of the treatment effect. For effects in the range of a 2- to 3-fold risk reduction relative to what has been achieved with recent protocols, our sample size calculations suggest that the latter approach is feasible and could answer key questions more quickly.

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